THE CONSTITUTION OF LAUROTETANINE

by

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University of Edinburgh.

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Vita.

I, Robert Silberschmidt was born in Zürich on 22.5.1901 as son of William Silberschmidt, now Professor of Hygiene and Bacteriology at the University of Zürich, and of his wife, Alice Rueff.

From 1908 to 1913 I attended the public schools of my native town; in 1913 I entered the grammar school (Literargymnasium) which I left in autumn 1920, after having passed the leaving examinations (Maturitätsexamen). I then went to the technical University in Zürich (Ecole polytechnique fédérale) where I took the course of Chemistry which lasted seven semesters (3½ years). I finished my studies with the work for the diploma as a chemical engineer with special training in electro-chemistry, which consisted in practical research during three months in the organic and inorganic technical laboratories and in the laboratory for electro and physical chemistry and during one month in the laboratories for analytical organic and inorganic chemistry and in oral examinations.

In spring 1924 I came to Edinburgh, and engaged in research under the supervision of Professor Barger, F.R.S., in the Department of Medical Chemistry, University of Edinburgh, until the end of April 1926.

CONSTITUTION of LAUROTETANINE

Laurotetanine was first isolated from Litsea chrysocoma and described by Greshoff[1]. He describes it as a crystalline base, soluble in potassium hydroxide solution, and giving a blue coloration with Fröhde's reagent, whilst with Erdmann's, it coloured the solution blue, changing into brown. Nitric acid colours the alkaloid solution reddish brown. Injected subcutaneously, the alkaloid produced tetanic convulsions.

Greshoff later found laurotetanine in about a dozen Lauraceae of which he gives a list in his publication, quoted by Gorter[2].

Filippo[3] started to investigate the chemical and physical properties of the base. The melting point is given as 134° C. The base is optically active, turning polarised light to the right. He gave the empiric formula as $C_{19}H_{23}O_5N$ and described the halides, sulphate, and picrate.

The formation of a phenylisocyanate showed the secondary character of the base, which was also proved by formation of the N-ethyl derivative.

By the Zeisel method three methoxy groups were identified, leaving two atoms of oxygen unaccounted for/

for. Neither hydroxylamine nor phenylhydrazine react with the base and therefore carbonyl groups could not be present. Filippo thought he had made a dibenxoyl derivative, which led him to assume the presence of two hydroxyl groups; but this assumption was incorrect, one of the benzoyl radicals having reacted with the secondary amine.

Later Gorter (4) investigated laurotetanine and its derivatives more thoroughly. According to him the crystalline base contains one molecule of water, which remains in the complex even after drying over sulphuric acid. It can only be removed by heating in vacuo over phosphorus pentoxide to 80°C. Gorter proved the presence of a single phenolic hydroxyl group by preparing the methyl ether of the base. This derivative, prepared with diazomethane, is insoluble in alkali and contains four methoxy groups. The formula was therefore settled as far as the nitrogen and oxygen constituents are concerned, as follows:

$$C_{16}H_{10} \begin{matrix} =NH \\ -OH \\ \equiv(OCH_3)_3 \end{matrix} (H_2O)$$

Gorter's investigations proceeded towards the determination of the structure of the carbon skeleton. Having formed the N-methyl methyl ether of the base, he was struck by the similarity of the chemical and physiological reactions of this compound with the reactions of glaucine (I) an isomer of dimethyl

laurotetanine/

laurotetanine whose constitution has been proved by synthesis out of laudanosine (Gadamer (5)).

Gorter made a thorough investigation of the respective salts of glaucine and the laurotetanine derivative, and was finally led to think that they must be very similar in their structure, but still distinctly different, none of the mixed melting points of the corresponding salts being constant. Optical isomerism was excluded by the fact that both bases are dextro-rotatory.

The oxidation of laurotetanine with potassium permanganate, which he effected, yielded 1.2. dimethoxy-benzene 3.4.5. tricarboxylic acid (II). Ascribing the colour reactions, which are the same with glaucine and dimethyl laurotetanine, to a similar position of the two methoxy groups in the benzene ring A of glaucine (I) he settled in his mind that there can only be a difference in the ring B. The only alternative following the formation of the acid II. was the formula III. for dimethyl laurotetanine, which Gorter calls iso-glaucine.

The oxidation of laurotetanine destroys the ring A. and therefore suggests the presence of the hydroxyl group of the phenolic base at the position 2 or 3 of the phenanthrene ring in iso-glaucine (III).

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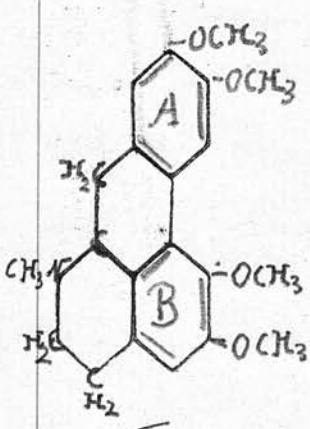

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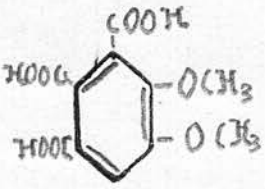

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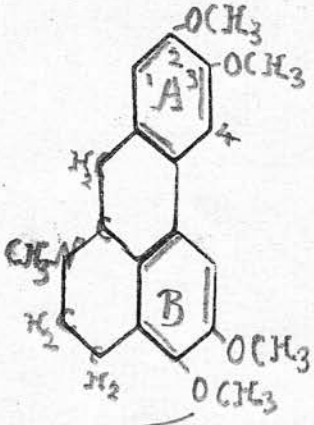

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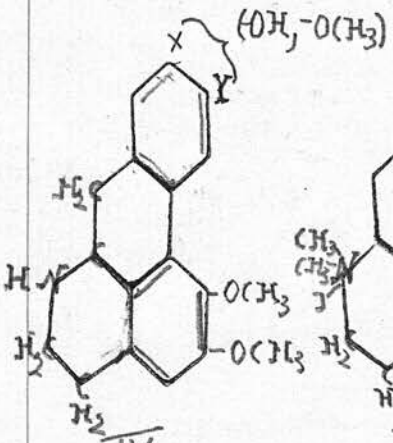

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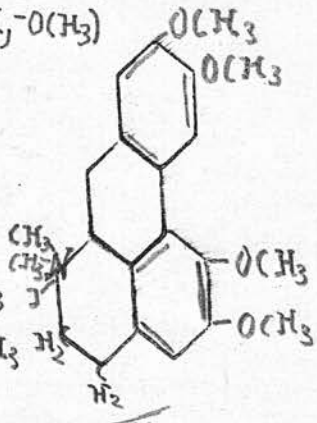

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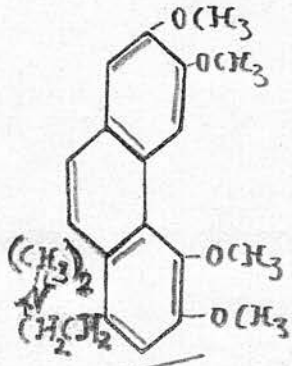

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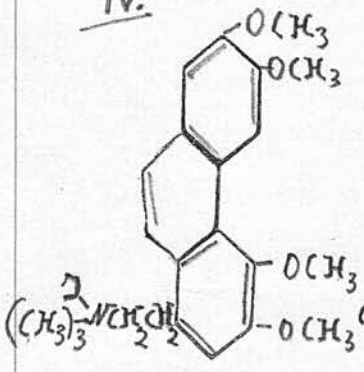

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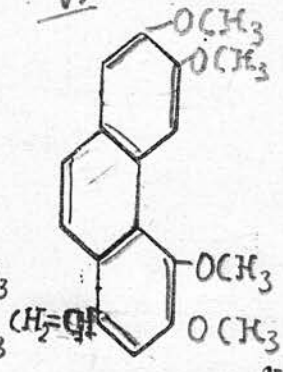

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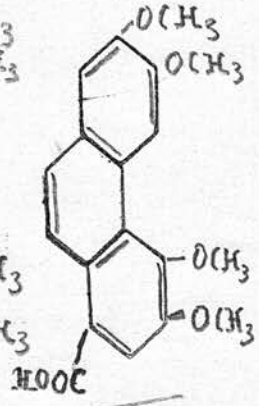

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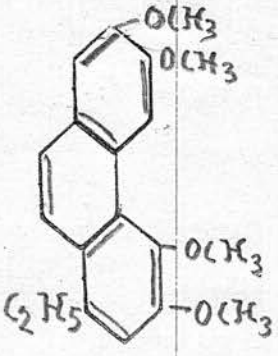


X.

In commencing further investigation into the constitution of laurotetanine, I had to keep in mind that the formula of "iso-glaucine" and the possible formulae of laurotetanine, put forward by Gorter, were in no case proved, although the comparison with glaucine and the oxidation product seemed to support his view, or part of it, at least. The i.2.dimethoxy-benzene 3.4.5 tricarboxylic acid, however, could be derived equally well from a phenanthrene ring substituted in the same way as glaucine.

Laurotetanine had not yet been treated by the method of exhaustive methylation (Hofmann decomposition) and, on the suggestion of Professor Barger, the investigation was started on these lines, which were likely to produce compounds already known or possible to synthesise.

Methylation of laurotetanine.

It is possible to methylate laurotetanine in alkaline methyl alcohol solution with methyl iodide. A preliminary experiment, however, showed that in this way the methiodide formed is partly decomposed by the alkali present, and two different compounds containing iodine were isolated. They were later on identified as two different stages in the Hofmann decomposition.

The direct method of methylation with methyl iodide was abandoned because of its unsatisfactory yields/

yields and because of the difficulty in deciding its progression. The dimethylation was carried out with diazomethane as Gorter[6] indicates for the formation of iso-glaucine. The dimethyl base, however, is very difficult to crystallise, and as a rule, I transformed it straight into the methiodide by adding methyl iodide in acetone or methyl alcohol solution. The methiodide was recrystallised and used as a starting point for the following reactions.-

Gorter describes the "iso-glaucine" methiodide as crystallising in needles, melting point 229° C. The melting point of glaucine methiodide given by Gadamer[7] is 219° C. and this is one of the reasons given by Gorter to prove the difference between the two bases. In spite of many recrystallisations in my case, the melting point could not be raised beyond 219° C. which corresponded with Gadamer's and not Gorter's results.

At the time of these investigations, glaucine had not yet been further decomposed, and it was therefore thought advisable to undertake afterwards the same decomposition with glaucine for the purpose of comparison. I extracted the glaucine from leaves and pods of Glaucium luteum.

Warnat[8] has since published an account of the exhaustive methylation of boldine which is an isomeride of laurotetanine ~~and of glaucine~~ with two phenolic hydroxy groups. He proved the identity of the decomposition/

composition products of dimethyl boldine and glaucine and also the identity of both these compounds. His results correspond with those obtained in my investigation of glaucine. My results showed the identity of the decomposition products of glaucine and also of iso-glaucine, and therefore the identity of these two bases.

The formula of laurotetanine is therefore settled with the exception of the phenolic group as shown by formula IV, the OH group being necessarily fixed to the ring A at X or Y.

Decomposition of glaucine methiodide.

Glaucine methiodide (V) was easily split into an optically inactive methine (VI) by heating it with alkali. The free base could be isolated and crystallised from ether, when the starting product had been pure, which was possible in the case of glaucine but not when starting with the laurotetanine.

On addition of methyl iodide the methine forms at once a crystalline methine methiodide (VII), melting at 274°-276° C. and very insoluble in practically every solvent tried. It decomposes, however, readily when heated with alcoholic potassium hydroxide, yielding trimethyl amine and 2.3.5.6.tetramethoxy.8.-vinyl- phenanthrene (VIII). The latter crystallised out during the reaction, forming almost colourless

rhomb/

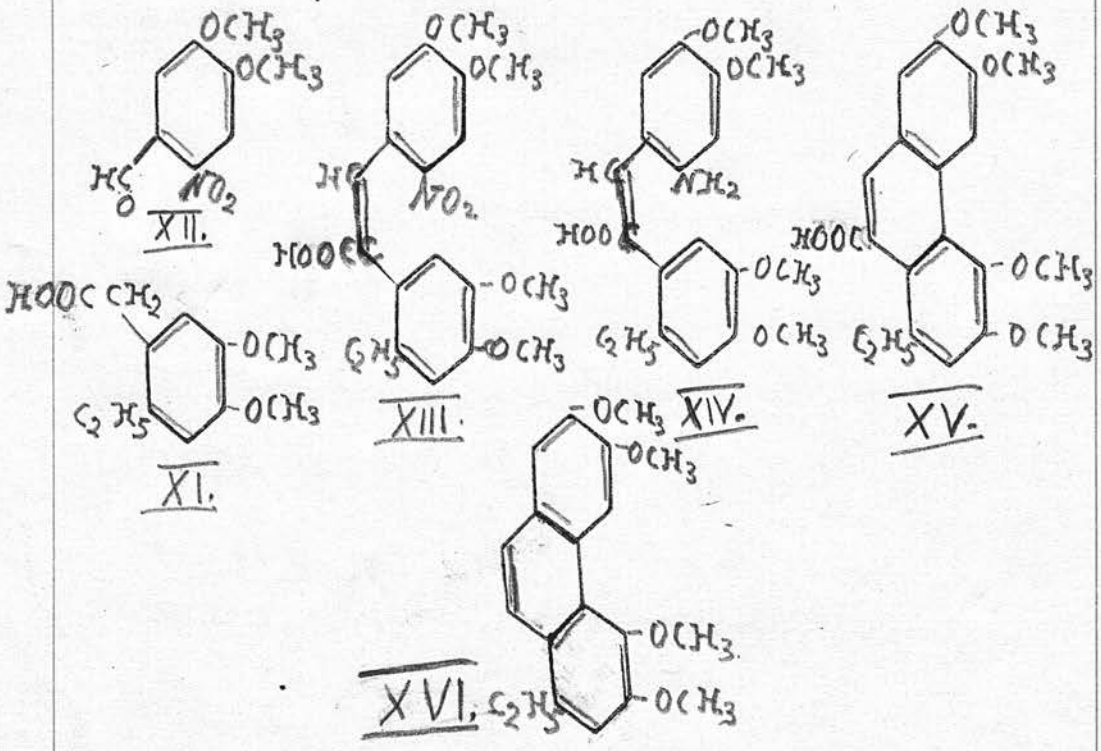
rhomboid shaped plates of melting point 142° C. Its unsaturated character is shown by decolorisation of potassium permanganate in cold solution. The vinyl compound is easily oxidised by permanganate to the carboxylic acid (IX), which crystallises in yellow lozenges.

To form a compound which can be synthesised by the method of Pschorr, it was first thought to split off carbon dioxide from this acid, thus forming 2.3.5.6-tetra methoxy phenanthrene. It was, however, impossible to remove it either by simple vacuum distillation, when the acid itself sublimed at high temperature, or with quick-lime, when the very small distillate could not be crystallised, or by heating it with glacial acetic acid, when a dark, oily, uncrystallisable residue remained. The fairly small quantity of vinyl compound left was therefore reduced with hydrogen and palladium into 2.3.5.6-tetra-methoxy-8-ethyl phenanthrene (X). The product, after purification by vacuum distillation and re-crystallisation, melted at 119-120° C.

Synthesis/

Synthesis of 2.3.5.6-tetra-methoxy-8-ethyl phenanthrene.

This synthesis follows the lines of the Pschorr synthesis of phenanthrene derivatives. A substituted nitro benzaldehyde and a phenylacetic acid derivative are linked together by the method used in the cinnamic acid synthesis. Then the nitro group which is in the ortho position to the bridge linking in one of the benzene rings is reduced, diazotised, and the nitrogen split off, thus forming the second link. In this case the two compounds required were: 3.4-dimethoxy-6-ethyl-1-phenylacetic acid (XI) and 3.4-dimethyoxy-6-nitro,1-benzaldehyde (XII).



They are condensed to form α-3.4-dimethoxy-6-ethyl-β-3.4.dimethoxy-6-nitrophenyl-acrylic acid (XIII). This acid is reduced to the corresponding amino acid (XIV) with/

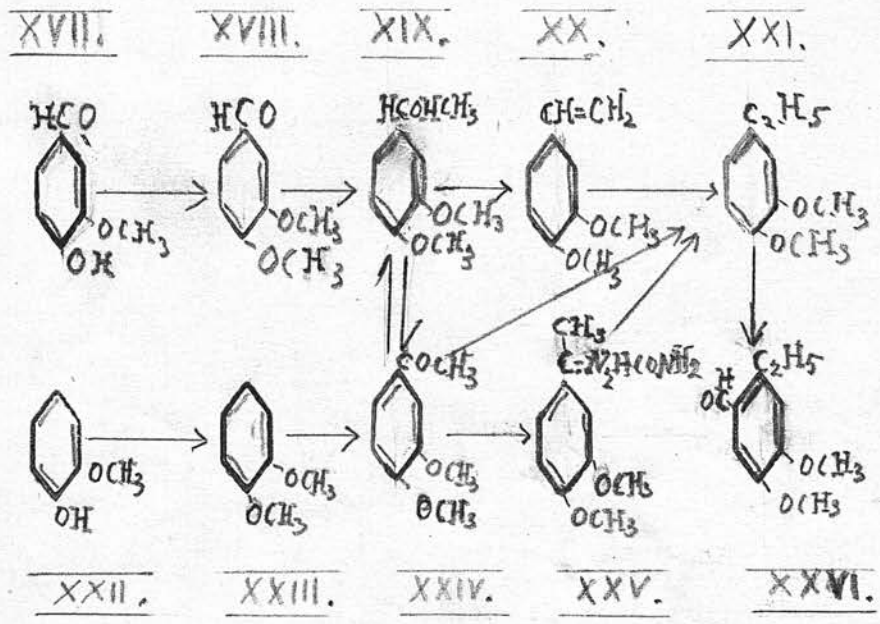
with ferrous sulphate. Diazotisation and reduction closes the phenanthrene ring, thus producing 2.3.5.6 tetra-methoxy-8-ethyl-9-phenanthrene carboxylic acid (XV).

The last step in this synthesis is the removal of carbon dioxide by vacuum distillation which yields the product required: 3.4.5.6.tetra-methoxy-8-ethyl phenanthrene (XVI).

The ethyl group in ortho position to the acetic acid radical in the phenylacetic acid derivative has the advantage of excluding another alternative for the ring closure, thus settling the position of the substituents in the phenanthrene complex.

Synthesis of 3.4.dimethoxy-6-ethyl phenyl acetic acid.

To prepare this acid first 3.4-dimethoxy ethyl benzaldehyde had to be synthesised. The different methods of preparing this compound are shown in the following scheme:



3.4.dimethoxy styrol (XX) has been prepared by Barger and Jowett[9] who started from vanillin (XVII). It is first methylated (XVIII) and then by Klages method[10] transformed into the dimethoxy-phenyl-methyl carbinol (XIX). This product can ~~either~~ be distilled in vacuo when it partly loses a molecule of water. It is better transformed into the chlorine derivative first, by passing hydrochloric acid through the ethereal solution of the carbinol and distillation after treatment with pyridine. (Mannich[11]).

Out of the styrol the ethyl compound (XXI) is formed by dissolving in alcohol and heating with sodium in excess. Mannich points out the easy polymerisation of the styrol compound when it is left in contact with aqueous acid solution. He started from guaiacol (XXII) which he methylated first, thus forming veratrol(XXIII). This he transformed into acetoveratrone by Friedel Craft's reaction with acetyl chloride and aluminium chloride (XXIV). The reduction into the carbinol (XIX) is effected by sodium and alcohol.

The first experiments which followed the method of Klages and in which vanillin was used as original substance, showed again the very rapid polymerisation occurring several times to practically the whole amount used. It was also observed when the styrol or carbinol was distilled and during reduction with sodium/

sodium and alcohol.

Although on two occasions a yield of 25-30% 1-ethyl.3.4.dimethoxy benzene was obtained (calculated from the methyl vanillin used), it was thought preferable to avoid the unsaturated stage by reducing aceto-veratrone (XXIV) straight into the ethyl compound, the ketone being either prepared by oxidation of dimethoxy phenyl methyl carbinol (from vanillin) or in better yield from guaiacol.

Two later methods of reducing ketones into the dihydro derivatives are in existence. One is the method, described by Wolff,(12) which consists of heating the hydrazone or the semicarbazone of a ketone in alcohol in the presence of sodium ethylate in a closed tube for five or more hours to about 200° when nitrogen, or nitrogen, ammonia and carbon dioxide are given off and a very good yield of the reduced hydrocarbon is obtained.

$$=CO + H_2N_2H_2 \longrightarrow =CN_2H_2 + H_2O$$

$$=CN_2H_2 \xrightarrow[\text{Catalist}]{NaOC_2H_5} =CH_2 + N_2$$

This reaction has the advantage that the original substance can easily be obtained crystalline and pure. Owing to the formation, however, of one molecule of nitrogen gas out of one molecule of hydrazone used, it requires (at least when done as Wolff describes it, who did it in small quantities) a very strong receptacle to stand the pressure resulting when large/

large quantities are used. No autoclave being available, this method had to be abandoned, although the high pressure seems rather a secondary feature which does not affect the reaction itself. The only reason for the use of a closed tube is probably the presence of alcohol as a solvent, thus producing close contact of the substance with the sodium methylate. Perhaps it is possible to find another solvent, boiling at or over 200° or to try to heat the mixture of semi-carbazone and sodium alcoholate in hydrogen or nitrogen atmosphere without solvent.

An experiment on a small scale with 4 grams of semi-carbazone yielded in this way 50% of reduction product, but I was unable to go further into the details of this reaction.

A second method which was then successfully adopted was the reduction with zinc amalgan and hydrochloric acid introduced by Clemensen (13). Clemensen showed the formation of unsaturated products in intermediary stages and therefore I feared polymerisation in my case. This assumption proved correct: when acetoveratrone is added at once to the zinc amalgam, as prescribed in the original method, and then heated with concentrated acid, two-thirds form a resinous, though almost colourless, oil, which distils at about 240° C under 10 mm. pressure, while only about one-third distils at 112° C. By adding the product little by little to the boiling hydrochloric acid solution (and therefore/

fore reducing with an excess of hydrogen) I was able to improve the yield to 70% of the theoretical.

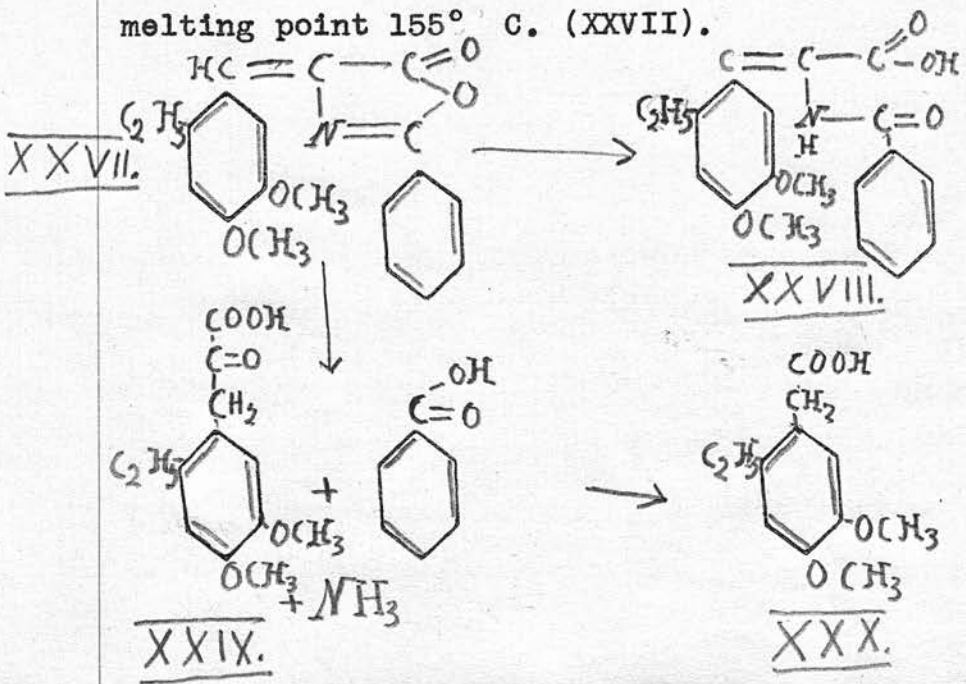
1.ethyl-3.4.dimethoxy-benzene (XXV) is a colourless oil, boiling in vacuo (9-10 mm) at 110-112° C.

3.4.dimethoxy-6.ethyl-1.benzaldehyde (XXVI) was prepared by Gattermann's method[14] for aldehyde synthesis, using hydrocyanic acid. It distils at 150° C. in a vacuum of 9 mm. and crystallises in rhomb shaped plates, whose melting point is 28° C. Its semicarbazone melts at 197-199° C.

3.4.dimethoxy-6.ethyl-phenyl-1.acetic acid.

Decker and Kropp[15] give a method for the transformation of benzaldehydes into the corresponding phenyl-acetic acids, which was followed in these experiments.

The aldehyde forms, on heating with hippuric acid, sodium acetate and acetic anhydride, a lactone which recrystallises in silky yellow needles of melting point 155° C. (XXVII).



Dimethoxy-ethyl-benzal-hippuric acid lactone is hydrolised by weak alkali into the corresponding acid (XXVIII), melting point 212° C. and by 30% potassium hydroxide into the 3.4.dimethoxy-6.ethyl phenyl pyruvic acid (XXIX), when ammonia is evolved and benzoic acid yielded as by-product. The oxidation with hydrogen peroxide in the cold yields as final product dimethoxy-ethyl-phenyl-acetic acid, melting point 67° C. (XXX) of which the potassium salt is used for the further synthesis as stated on page 9.

Preparation of nitro-methyl vanallin.

The nitration of methyl vanillin is described by Pschorr (16). Methyl vanillin is added to a cooled solution of concentrated nitric acid in which it is soluble. On addition of ice water the nitro-compound is precipitated out.

The methyl vanillin used was prepared by a method slightly different from those quoted in the literature and gave quantitative yields of pure substance without recrystallisation. No solvent was used, but both concentrated potassium hydroxide and dimethyl sulphate were added slowly to the well-stirred/

stirred aldehyde, which was previously melted on a water-bath. This method worked also in similar cases, when aldehyde groups rendered methylation difficult.

Ethoxy-trimethoxy-phenanthrene.

With the intention of settling finally the position of the phenolic group in laurotetanine the ethyl ether of this base was prepared with a quantity of the alkaloid which reached this laboratory only near the end of these investigations. The ethylation was carried out with ethyl toluene sulphonate and the ethyl ether, which could only be crystallised as the iodide, was then transformed straight into the methiodide. The further decomposition was exactly analogous with the reactions of the methyl derivative.

There are two possibilities for the position of the hydroxy group, and therefore only two alternatives for the ethoxy-trimethoxy phenanthrene compound, formed by Hofmann decomposition, namely:

2.ethoxy-3.5.6.trimethoxy-8.ethyl-phenanthrene (XXXI)

or

3.ethoxy-2.5.6.trimethoxy-8.ethyl-phenanthrene (XXXII)

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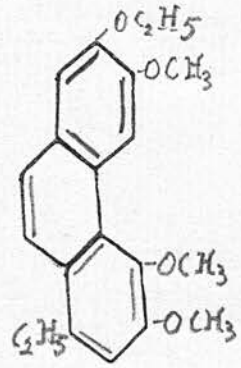

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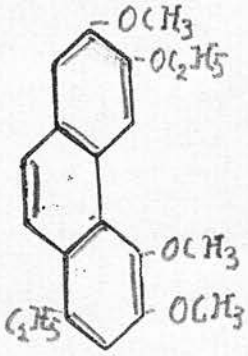

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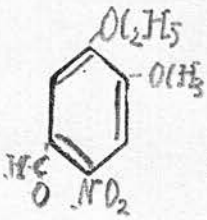

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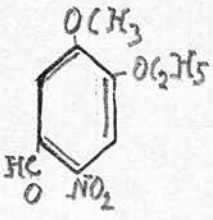


XXXIV.

For the synthesis of both these compounds the phenyl acetic acid part (forming ring B. after linking up) is the same as in the synthesis of the tetra-methoxy-ethyl-phenanthrene whilst the nitro-aldehyde, which is needed, is either nitro-ethyl-vanillin (XXXIII) or nitro-ethyl-iso-vanillin (XXXIV).

For the purpose of synthesis of one of these compounds the 6.nitro-3.ethoxy-4.methoxy-benzaldehyde (XXXIII) was prepared by nitrating ethyl-vanillin (formed by ethylation of vanillin with ethyl iodide in alkaline solution) with slightly fuming nitric acid. The nitro-ethyl-vanillin forms yellow crystals melting at 159-160° C. and sublimises slowly above 110° C. The phenyl hydrazone which is coloured strongly has a melting point 202° C.

EXPERIMENTAL.

Laurotetanine - $C_{19}H_{21}O_4N.(H_2O)$.

The preparation of the alkaloid was different from the method used by Gorter (4).

The bark of Litsea cubeba, citrata grown in Sumatra, was first powdered and extracted with alcohol in the works of Messrs Duncan, Flockhart and Co., and the concentrated extract, which was about 10% of the original quantity and formed a thick, dark tarry mass, was sent to this laboratory. The extract was brought into solution by boiling with about two-thirds of its weight of glacial acetic acid. The concentrated liquid was then poured into about 5-6 parts of water, which was vigorously stirred, when the insoluble nonalkaloidal portion was to a large extent precipitated. (Precipitate A)

After filtering through a folded filter, the brown solution was neutralised by addition of concentrated ammonia so as to remain still slightly acid to litmus. The precipitates formed were white at the beginning, but their quick darkening showed rapid oxidation. The solution was filtered and ammonia added until in acid solution no more precipitation occurred. Then the clear colution was made slightly/

slightly alkaline by addition of more ammonia and a voluminous pale yellow precipitate fell down, was collected on a Buchner funnel and washed thoroughly, so as to get rid of excess ammonia.

This precipitate of crude alkaloid was dried on porous plates in vacuo. It easily darkened when the ammonia was not washed out completely. The precipitate$_A$ formed after pouring the glacial acetic acid into water was once more extracted by dissolving it again in this solvent and treating it in the same way as the main portion. The dried crude alkaloid was afterwards mixed with about the same amount of sand and extracted with ether in a Soxhlet apparatus for several days. Soon a lightly coloured substance separated out of the solution. It was recrystallised out of acetone. The formation of the crystals was started by addition of a few drops of water to the oncentrated solution. The mother liquor was dark and the crystals were slightly brownish in colour. It was not possible to remove the colouring impurities completely. A few pure white crystals of laurotetanine crystallised out of the cooled ethereal extract, after standing for about a day. These crystals showed the melting point given in the literature, melting in the water of crystallisation from 124-134° C., but there was no darkening in the light as Gorter states, neither when left in the open air nor in solution.

The/

The precipitates formed before complete neutralisation of the acetate solution contain possibly other alkaloidal substances whose acid properties would be increased by a larger number of phenolic groups present. They are, however, easily oxidised and therefore difficult to investigate.

The yield of laurotetanine was about 0.3-0.4% of the weight of the bark.

Preliminary experiments.

0.5 grams laurotetanine were heated on the water-bath with 2 grams of methyl iodide in methyl alcohol: 0.5 grams sodium hydroxide in 3 c.c. of water added drop by drop kept the reaction continuously alkaline. After four hours, excess of methyl iodide was added and the solution heated till the alkaline reaction disappeared. After filtration and concentration water was added when the liquid became strongly turbid. It was acidified and extracted with chloroform. After evaporation of the chloroform, an oil remained, which solidified on cooling. After washing it twice with ether, which practically did not dissolve anything, the substance was heated with acetone. Partial solution occurred, and colourless needles separated out from the solution. These needles were insoluble in cold water and almost insoluble in ether; they

can/

can be recrystallised out of hot water and hot alcohol. Melting point 219° C.

Ammonia did not affect the crystals, whilst on heating with sodium hydroxide an amorphous precipitate was formed after decomposition of the salt. The presence of iodine was shown by a yellow silver iodide precipitate with silver nitrate.

In a second experiment of the same kind a crystalline precipitate was formed in the alkaline alcoholic solution itself. This was different from the first precipitate by its even more pronounced insolubility in alcohol and water; its melting point was 278° C. It also contained iodine.

In both experiments, the substances recovered as definite products were less than 50%of the original quantities. - The methylation was then effected with better yield by the use of diazomethane, when the identity of the products was easily established.

Dimethyl-laurotetanine-methiodide. (Iso-glaucine-methiodide). $C_{22}H_{28}O_4NH$.

1 gram laurotetanine was left overnight in 10 c.c. of methyl alcohol with an ethereal solution of diazomethane prepared from 6 c.c. of nitroso-methyl-urethane in 60 c.c. of ether and 7 c.c. of 25% alcoholic potassium hydroxide. At the beginning nitrogen was freely evolved. The next day the solution was evaporated down (in a fume cupboard) to get rid/

rid of excess diazomethane. The residue was dissolved in hydrochloric acid and the dimethylated base set free by addition of sodium hydroxide in excess and exhausted with ether. The base which remained after drying and evaporation of the ether solution formed a yellowish syrup. It was at once transformed into the methiodide by addition of methyl iodide in excess in methyl alcohol solution. Bundles of colourless needles separated overnight; they were identical with the needles of the first experiment and proved ~~them~~ to be the methiodide of dimethyl laurotetanine. The yield of the methiodide was 60%. The melting point remained at 219° C. in spite of recrystallisation (Gorter 226° , glaucine methiodide 219°). This quaternary iodide like most iodides of laurotetanine and glaucine derivatives was very insoluble in cold water and also in many organic solvents. It was possible to extract it completely out of aqueous solution by shaking with chloroform.

Dimethyl laurotetanine methine. $C_{22}H_{28}NO_4$

500 mgs. of methiodide were heated for 5 hours under reflux in 40 c.c. of a 10% solution of alcoholic potassium hydroxide. The solution became slightly red. It was then concentrated and water added, when a white oily base separated. On neutralisation with acid colourless plates (rhomb shaped) were formed. These were very insoluble in water/

water and alcohol and melted at 265° C. These crystals are the iodide of the methine.

For analysis of the iodine content of methine iodide, silver nitrate was added to an ammoniacal solution so as to set free the base first. Afterwards the solution was made acid with nitric acid (so as to form the nitrate of the base) and heated on the water-bath. The solution turned a deep red colour. The silver iodide precipitate was then filtered through a Gooch filter, dried, and weighed in the usual way. 0.1024 grams substance gave 0.0483 grams AgI , corresponding to 0.0254 grams I.
Found 26.2% I. Calculated for $C_{22}H_{28}NO_4.HI$ 26.6% I.

The free methine was obtained after treatment of the iodide with ammonia and extraction with ether. It could not be crystallised either out of solvents or after vacuum distillation in a test tube, when it formed yellowish oily drops, appearing at a bath temperature of over 200° C. The base seemed to be more soluble in cold water than in hot, and gave a pink coloration to the solution. This colour reaction and the portion insoluble in hot water were due to impurities as decomposition of the pure glaucine derivative did not show these phenomena. In this case the methine could be crystallised. The impurities seemed to be very difficult to separate from the products of methylation and are probably responsible/

responsible in Gorter's investigation for the lowering of the melting points of his iso-glaucine salts. The methine yield from 500 mgms. of methiodide was 400 mgms., corresponding to 80% of the theory.

Dimethyl-laurotetanine-methine-methiodide

($C_{23}H_{31}NO_4I$)

On adding methyl iodide to the ethereal solution of the methine, white needles of the corresponding methiodide separated out, only very slightly soluble in hot water. The melting point was 276° C.

8-Vinyl-2.3.5.6.tetramethoxy-phenanthrene.

$C_{20}H_{20}O_4$.

370 mgms. methine methiodide (.75 millimol) were heated with 40 c.c. of 10% methyl alcoholic potassium hydroxide under a reflux on the water-bath. A slow air current was passed over the solution and afterwards led through a solution of N/10 hydrochloric acid, with methyl red as indicator. The trimethylamine set free by the reaction was thus neutralised and allowed to control the progress of the decomposition.

After 6 hours about 90% of the theoretical quantity of the base (6.5 c.c. N/10 acid) was set free and the reaction was stopped. The alcoholic solution was concentrated, when there separated out crystals which were considerably increased by the addition/

addition of water and neutralisation with sulphuric acid. They were extracted with ether and recrystallised out of hot alcohol. The compound formed slightly pink coloured plates of rhomb shape melting at 142° C. Yield = 140 mgms. = 60% theory.
It decolorised potassium permanganate in cold acetone solution,

Analysis (micro-analysis by Feinchemie, Tübingen).
3.275 mgms. of substance gave 8.890 mgms. CO_2, 1.84 mgms. H_2O.
3.660 " " " 9.930 " " 2.09 " "

Found C = 74.05%, 74.02%. H = 6.29%, 6.39%.

for $C_{20}H_{20}O_4$
Calculated C = 74.0=% H = 6.17%.

Trimethyl-amine:

The solution of trimethyl-amine hydrochloride was evaporated to dryness. Platinum chloride was added and a yellow crystalline precipitate was formed, which was recrystallised out of alcohol, the melting point with decomposition being at 253° C. The platinum content of 4.7 mgms. of the platinum complex salt was 1.75 mgms. This corresponds to 37.2% of Pt. Calculated for $(CH_3)_3N\ H\ PtCl_6$ - 36.7%. The substances were weighed on a balance of which the limit of accuracy was 0.1 mg. The difference between result and calculation does not exceed the possible error of weighing.

Tetra/

Tetramethoxy-phenanthrene carbonic acid.

($C_{19}H_{18}O_6$)

5.108 grams of the vinyl compound are dissolved in 10 c.c. of acetone. During one hour 0.175 gms. of $KMnO_4$ (corresponding to 5 O) are added whilst the solution is kept cool. The permanganate is reduced. The acetone solution was filtered, concentrated and diluted with sodium carbonate. The remaining manganese dioxide was reduced in aqueous bisulphite solution, made alkaline and added to the first solution, which was then extracted with ether, a small quantity of unchanged vinyl product being recovered. After acidification with hydrochloric acid, the tetramethoxy-phenanthrene carbonic acid was extracted with ether. It forms yellow crystals not very soluble in ether, recrystallising out of acetone and a little water and from benzene and ligroin.

Melting point = 215° C.

Equivalent: The acid is dissolved in N/5 sodium hydroxide solution and the excess titrated with a solution of N/25 oxalic acid, phenolphthalein being used as indicator. In neutral solution the acid changed slightly the colour from brownish yellow to a lighter shade and started separating in gelatinous form; this hindered the determination of the neutral point.

0.2277 grams of acid correspond to 16.8 c.c. N/25 oxalic acid.

Calculated for $C_{19}H_{18}O_6$ the quantity needed is 16.6 c.c. " " "

Comparison with the exhaustive methylation of Glaucine.

Preparation of glaucine ($C_{21}H_{25}O_4N$).

The glaucine used for these comparative reactions was extracted out of Glaucium luteum, of which green plants were obtained from the Royal Botanic Garden, Edinburgh, and a large supply was collected at Cockburnspath.

The extraction of this plant is described by N. Fischer (17). His indications of the solubility of different salts of glaucine led to a very much shorter way of isolating the base by precipitation as the iodide. The iodide is less soluble in water than the chloride, and almost as insoluble as the precipitate with Mayer's reagent (limit of visible precipitation occurs in concentration 1:10000).

10 kilograms of the leaves and pods of Glaucium luteum, in quantities of 2 kilo each, were first heated to boiling in water, which just covered the plants. After cooling, the leaves were passed through a mincer, whilst the pods were cut into small pieces, and both added to the original solution. Water was added so as to get the suspension easily stirred. After addition of about 2% of glacial acetic acid the suspension was stirred for 2-3 hours. The extract was filtered through gauze, the residue pressed out and left standing overnight in a fresh quantity of water, which was filtered the next morning and used for the extraction of a

further/

further portion.

The filtered extracts were concentrated in the vacuum to half syrupy consistence and then filtered through glass-wool. Potassium iodide crystals in excess were dissolved in the hot solution and the vessel was allowed to stand for two days. A layer of brownish crystals covered the bottom of the glass beakers. This allowed decantation of the solution through a filter, and then the precipitate was washed and collected. The brown crystals were easily re-crystallised out of a large quantity of alcohol and separated in long silky needles which were slightly pink coloured and melted at 243° C.

The yield of 35 gms. of glaucine from 10 kg. of fresh leaves corresponded to 0.2% of glaucine isolated out of pods and leaves.

The filtrate after separation from glaucine iodide was made alkaline with ammonia. A small precipitate was found, which gave the colour reactions of protopine (as indicated by Fischer[17]. It was neglected.

For the preparation of glaucine the iodide was shaken in aqueous ammonia solution with ether, when the insoluble salt disappeared, leaving an almost colourless ethereal layer, whilst the aqueous part contained the impurities, which remained with the iodide.

The ethereal solution left, after drying and slow evaporation, colourless prisms, which melt at 114-115°C.

The/

The melting point could be raised by repeated recrystallisation out of ether to 118-119° C.

Glaucine acetate. ($C_{21}H_{26}NO_4HOOC.CH_3$)

This was formed by addition to the acetone solution of the pure base a small excess of glacial acetic acid. Rhomb-shaped crystals, soluble in ether and melting at 96° C. were formed.

Glaucine methiodide ($C_{22}H_{28}O_4NI$)

6.7 grams of glaucine left overnight with 10 grams of methyl iodide in acetone solution yielded quantitatively glaucine methiodide.

(1) Melting point ..... 219° C.
(2) Mixed melting point with dimethyl laurotetanine methiodide..... 219° C.

Glaucine methine ($C_{22}H_{27}O_4N$)

9 grams of the methiodide were heated in 70 c.c. of methyl alcohol with 7 grams of potassium hydroxide. The solution remained almost colourless. After concentration and neutralisation the iodide of glaucine methine is formed.

(1) Melting point ..... 264° C.
(2) Mixed melting point with the laurotetanine derivative..... 263° C.

The sulphate of glaucine methine, formed by addition of sulphuric acid tothe free base, crystallises in rhomb-shaped plates, melting at 189-190° C. It reacts acid.

Analysis:
The sulphuric acid present in glaucine methine sulphate, which was recrystallised out of methyl alcohol/

alcohol and water and dried at 100°, is precipitated by $Ba(NO_3)_2$; the barium sulphate is filtered and washed, the filter ignited in a crucible ~~was treated to red heat~~ and weighed. The result showed the the salt to be an acid sulphate.

0.0960 gms. of methine sulphate gave 0.0486 gms. of $BaSO_4$ = 21.2% H_2SO_4

$C_{22}H_{27}O_4N.H_2SO_4$ contains 20.9% "

Glaucine methine acetate was prepared similarly to the acetate of glaucine by addition of glacial acetic acid in slight excess to the acetone solution of the free base. The crystals formed were soluble in ether and not very soluble in cold water. Melting point 91°C.

Glaucine methine methiodide ($C_{23}H_{30}O_4N_3$)

This very insoluble salt crystallised out at once after adding methyl iodide to the methine base.

Melting point ..... 278° C.
Mixed melting point with dimethyl laurotetanine methine methiodide..... 276° C.

8.Vinyl-2.3.5.6.tetramethoxy-phenanthrene.

The splitting off of trimethyl amine was in every way the same as in the case of the laurotetanine compound, the compound having a melting point 142° C. The mixed melting point showed no depression.

2.3.5.6. tetramethoxy-phenanthrene-8.carboxylic acid was prepared out of the glaucine compound as described in the case of the laurotetanine derivative, showing practically the same melting point (214° C.) and showing/

showing no difference when both substances were mixed.

Preparation of glaucine iodide out of laurotetanine.

A small quantity of laurotetanine(which was completely pure)was dimethylated with diazomethane, as described and then transformed into the iodide. The iodide obtained had the same melting point as the iodide of glaucine (243° C.) and had no lowering effect on the mixed melting point with glaucine iodide. This fact is different from the quotations given by Gorter,(4a) who prepared different halides of both bases, which seemed to be distinctly different.

Table/

Table of Melting Points of the Derivatives of Laurotetanine and Glaucine.

(Compared with the results given by Warnat for dimethyl-boldine)

Derivative	Dimethyl laurotetanine. M.Pt.	Glaucine M.Pt.	Mixed melting point.	Mixed melting point given by Warnat.
Hydroiodide	243	243	243	239-241
Methiodide	219	219	219	221
Methine-hydraiodide	264	264	263	
Methine methiodide	276	278	276	276-278
Tetramethoxy-vinyl-phenanthrene	142	142	142	142-143
Tetramethoxy-phenanthrene carboxylic acid	215	214	214	

This establishes the identity of glaucine and dimethyl-laurotetanine.

2.3.5.6.tetramethoxy-8.ethyl phenanthrene.

After having established the identity of glaucine and isoglaucine, it was possible to use the glaucine derivative instead of laurotetanine, the quantity of laurotetanine available being used up after the unsuccessful attempts to form tetramethoxy-phenanthrene out of the carbonic acid.

0.485 grams ($\frac{3}{2}$ millimols) of the vinyl compound were dissolved in the minimum amount of glacial acetic/

acetic acid, colouring the solution strongly red. The solution was brought into an evacuated flask, in which 40 mgms. of palladium chloride in a little acetic acid,(after addition of gum arabic) had already been reduced. The apparatus was then filled with hydrogen and shaken mechanically when the absorption of hydrogen could be controlled in a burette. Within 20 minutes about 35 c.c. of hydrogen gas were absorbed, and the decrease in the burette stopped almost completely.

The solution was washed into a beaker. On addition of water a brown precipitate of palladium and reduced substance was formed and filtered. The filtrate and the precipitate were extracted with ether several times. The ether extract after evaporation of the solvent was recrystallised out of methyl alcohol. The ethyl compound crystallised out after a short time, being insoluble in cold methyl alcohol. Yield - 380 mgms. = 79% of theory.

For purification the crystals were redistilled in the vacuum with the bath temperature at 190-205 C. Colourless drops condensed on the walls of the flask, crystallising out after a short time. They were redissolved in methyl alcohol out of which long narrow plates crystallised out, melting at 120° C.

Synthesis of Phenylacetic Acid.

(a) Preparation of aceto-veratrone out of vanillin.

Methyl-vanillin. $C_6H_3(OCH_3)_2COH$. (18,19,20)

The following method, adopted after some less successful attempts, gave a quantitative yield of pure methyl-vanillin, and was also successfully used in other cases of methylations, especially of aldehydes, which are likely to cause secondary reactions.

1 mol of vanillin (~~125~~ 152 gms.) is melted, without solvent on a steam-bath in a closed beaker or wide-necked bottle, provided with a stirrer, a reflux condenser and two dropping funnels. When the vanillin is melted one starts, whilst stirring vigorously, to drop in a solution of 1.5 mol (82 gms) of potassium hydroxide in 120 c.c. of water at a fairly quick rate (2 drops per second) and 20 seconds afterwards starts the addition at the same rate of 1.25 mol (160 c.c.) of dimethyl sulphate, which has been standing over potassium carbonate and is neutral to Congo paper. The heating is soon stopped, when the reaction keeps the temperature high; the closed system with condenser is mainly a protection against vapours containing methyl sulphate, due to the vigorous reaction. The reaction mixture is slightly reddish brown in colour, which is a proof of its being alkaline, a change to green indicating acidity.

When/

When about three-fourths of the solutions are dropped in, the stirred liquid becomes turbid, separating in two layers. After about 20 minutes, the reaction is finished. The liquid is poured into a porcelain basin where the upper layer which is only faintly coloured crystallises after cooling into a hard, completely white mass of methyl vanillin which has a melting point of 43° C. The aqueous layer is colourless. The methyl vanillin, after washing with water and drying, can be used as such for most reactions. Yield: 165 gms.

For use in the Grignardreaction the methyl vanillin was especially dried. It was extracted with ether as oily layer, before crystallisation and washed with water, dried with sodium sulphate, and the ether distilled off. The remaining oil was left in a basin in a vacuum desiccator, where it crystallised after a short time.

3.4-Dimethoxy-phenyl-1.methyl carbinol. (21)

$C_6H_3(OCH_3)_2COCH_3$ (Barger and Jowett Klages (22))

To a solution of Grignard reagent made by addition of 4.85 gms. of magnesium ribbon to 26 gms. of dimethyl iodide in 200 c.c. of dry ether ($\frac{1}{5}$ mol of each), and cooled to -2° C., 33 gms. of methyl vanillin in ether solution are added with very vigorous shaking. The voluminous precipitate is collected on a dry Buchner funnel, the ether solution with/

with unchanged substance being filtered off. The addition product is then poured on ice and decomposed by addition of sulphuric acid. It is then extracted with ether. The extract is shaken several times with bisulphite solution so as to remove unchanged aldehyde, which forms a white addition product fairly soluble in water.

After drying the solution, the ether is distilled off and the residue is weighed. Yield - 25 gms. of carbinol, corresponding to 60% of the theory.

The product is at once oxidised without purification to form aceto-veratrone[23] - $C_6H_3(OCH_3)_2COCH_3$ 18 gms. of carbinol were poured into a solution of 30 gms. sodium bichromate in 120 c.c. of water to which 25 c.c. of concentrated sulphuric acid were added. The temperature rose from originally 30° C to 55° C. and the flask had to be cooled. The colour changed to brown, the ketone separating as an oil, which was estracted with ether, washed with sodium hydroxide and water, concentrated and distilled in the vacuum (9 mm) at a boiling point 158° C. The distillate, a colourless oil, solidified soon after cooling, forming crystals which melted at 50° C. Yield - 13.5 gms. of ketone = 80% of theory.

(b) /

(b) Acetoveratrone prepared out of guaiacol. (24)

This method gave a better yield and avoided the Grignard reaction, in which the methyl iodide used in fairly large quantities, is expensive. Crystalline guaiacol had to be used to obtain pure products, whilst the guaiacol B.P. seems to be a mixture of constant boiling point, difficult to purify.

Veratrol $C_6H_4(OCH_3)_2$.

The methylation with dimethyl sulphate and potassium hydroxide was similar to the method indicated for methyl vanillin. 220 grams of guaiacol were used. After methylation an oily, colourless layer separated out of which long prisms separated, which could be filtered off. The remainder was extracted with ether and distilled. Boiling point 203-205° C. The yield was 227 grams of veratrol = 95%.

Acetoveratrone. $C_6H_3(OCH_3)_2.COCH_3$.

180 gms. of veratrol were dissolved in 440 c.c. of carbon disulphide by addition of 139 gms. of acetyl chloride. The flask was cooled with ice and 180 gms. of freshly powdered aluminium chloride were added slowly, a vigorous reaction taking place at the beginning. At the end the flask is heated for a short time to 50° C. The reaction product, a dark red/

red precipitate was separated by filtration from the solution and then decomposed by ice to which it was added in small portions. The aceto-veratrone dissolved in the carbon disulphide still present, forming a yellow layer, which was separated from the aqueous solution, and was shaken with about 50 c.c. of sodium hydroxide solution and allowed to separate overnight. Large rhomboidal crystals were formed the next morning, and were collected, and dried whilst the carbon disulphide solution was isolated, concentrated and the remaining oil distilled in the vacuum. The boiling point was the same as for the compound prepared by oxidation, 158°C.(9 mm), the distillate crystallising forming a hard, colourless crust of rhomb-shaped plates. Yield: 188 gms. = 81% of theory.

The semicarbazone formed by adding 0.5 gms. of aceto-veratrone, dissolved in 1 c.c. of alcohol, to a solution of 0.5 gms. semicarbazide chloride and 0.5 gms. potassium acetate in 2 c.c. of water melted at 223°C. (Mannich gives the melting point as 211°C.).

1-ethyl-3.4.dimethoxy-benzene.[25] $C_6H_3(OCH_3)_2.C_2H_5$

720 gms. of granulated zinc were left for 1 hour in a solution of 72 gms. of mercuric chloride in 1420 c.c. of water, forming thus zinc amalgams. The liquid is then poured off and the zinc covered with/

with hydrochloric acid of the concentration 1:3. The liquid was heated to boiling under reflux, and hydrogen was evolved vigorously. 180 gms. of aceto-veratrone were added within an hour, and the boiling continued for 5 hours, every hour 50-100 c.c. of the acid being added again.

The oily top layer was then separated, the solution extracted three times with ether, and the separated and extracted oil distilled in the vacuum. At 110-112° C. (9 mm.) 3.4.dimethoxy-1.ethyl-benzene came over. Towards the end the temperature rose at once to 230-240° when a polymerised product distilled over. The yield obtained was 110 gms., equal to 68% of the theory. Dimethoxy-ethyl-benzene is an oil and could not be crystallised. The polymerisation allowed a clear separation of the ethyl compound from the compounds not completely reduced, because of the large space between the two boiling points, and in this respect it was considered to be rather an advantage. The distilled dimethoxy-ethyl-benzene did not reduce permanganate.

3.4.dimethoxy-6.ethyl-1.benzaldehyde.

$C_6H_2(OCH_3)_2.C_2H.CHO$. (Gattermann[26]).

This aldehyde was prepared following the directions for dimethoxy-methyl-benzaldehyde. The reactions were carried out in a well ventilated fume cupboard.

54 gms. of dimethoxy-ethyl-benzene were dissolved in 75 gms. of anhydrous benzene.in a conical flask. The flask was cooled with ice and 60 gms. of freshly powdered anhydrous aluminium chloride were slowly added. The liquid became slightly brownish in colour. 55 gms. of pure hydrocyanic acid, prepared out of a saturated solution of potassium sodium cyanide and 50% sulphuric acid, were then added at once, and the flask closed with a stopper, connected with a reflux condenser and a wide glass tube which reached into the solution. Dry hydrochloric acid was passed for 3 hours through the well cooled solution, which slowly became saturated with it. Then the ice was removed and the flask heated in a water-bath to 30°C. for half an hour. The passage of hydrochloric acid was ceased and the reaction mixture left to itself overnight.

The imide chloride formed was decomposed (the next day) by pouring the mixture into ice , when the formed crystals and the aluminium chloride reacted with the water, leaving an oily layer behind. For completion of the decomposition and removal of the benzene and the excess hydrocyanic acid, as well as of unchanged dimethoxy-ethyl-benzene, the liquids were brought into a round bottom flask and steam passed through for an hour.

The aldehyde formed, which remained as a brownish oil at the bottom of the flask, was extracted with/

with ether and after removal of the solvent distilled in the vacuum. It distilled as colourless liquid at 150-159° C. (9-10 mm). Only after long standing it crystallised in plates, melting at 28-30° C. It is very soluble in alcohol, ether, benzene and ligroin. To purify it for combustion, the aldehyde was redistilled in the vacuum.

0.2127 gms. of dimethoxy-ethyl-benzaldehyde gave 0.1356 gms. H_2O and 0.5277 gms. CO_2.

Corresponding to 7.13% H_2 and 67.7% C.

Calculated for $C_{11}H_{14}O_3$: 7.26% H_2 and 68.0% C.

The yield, 40 gms . of aldehyde corresponds to 68% of the theory.

The semicarbazone, formed by addition of 0.5 gms. of the aldehyde in ice of alcohol to 0.5 gms. of semicarbazide chloride and 1 gm. of potassium acetate in 3 c.c. of water crystallised out after evaporating the alcohol present. It forms colourless crystals; melting point 197-199° C.

Oxidation of 3.4.dimethoxy-6.ethyl-1.benzaldehyde.

To 1.94 gm. ($\frac{1}{100}$ mol) of the aldehyde were added in sodium hydroxide solution 7.38 gms. ($2\frac{1}{3}$ equivalent) of potassium permanganate in 140 c.c. of water (5% solution). The flask was finally heated on the water-bath until the red colour had disappeared. The solution was then saturated with sulphur dioxide to reduce the manganese dioxide formed/

formed. The solution being thus acidified, white crystals of an acid separated out, which were extracted with ether after removal of the excess sulphur dioxide on the steam-bath. The acid was recrystallised out of dilute alcohol and dried at 120°. It has a melting point of 138° C.

Equivalent: The acid was dissolved in about N/70 sodium hydroxide and the excess alkali titrated with acid of about the same strength.

0.0128 gms. of the acid required 4.95 c.c. of 0.0123 NaOH.

This corresponds to an equivalent of 210.5.

This corresponds to the equivalent of dimethoxy-ethyl-benzoic acid.

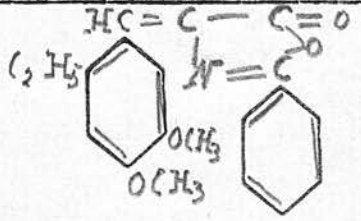
Calculated for $C_{11}H_{14}O_4$ the equivalent is 210.0.

Formation of 3.4.dimethoxy-6.ethyl-1.phenyl-acetic acid.

$C_6H_2(OCH_3)_2.C_2H_5.CH_2COOH$.

(Method of Kropp and Decker [27], Cain, Simonson and Smith [28], Haworth, Perkin and Rankin [29]).

3.4.dimethoxy-6.ethyl-1.benzal-hippuric acid lactone.



39 gms. of dimethoxy-ethyl-benzaldehyde were heated for 40 minutes with 40 gms. of hippuric acid in 82 c.c. of acetic anhydride, 16 gms. of powdered anhydrous sodium acetate being added. A clear yellow solution is formed out of which, before cooling down, bright yellow needles crystallise out, transforming soon the solution into a semi-solid mass. The excess acetic anhydride is removed by washing the formed lactone with a large quantity of ether. The ether extract leaves behind after recovering the solvent a brown substance, which, after neutralisation with sodium carbonate and recrystallisation out of alcohol, yields a few more lactone crystals. The main part, after washing with ether, is treated with water to remove the sodium acetate and then recrystallised out of hot alcohol in which it is not very soluble. The recrystallised lactone melts at 155° C.

A combustion of the compound (dried at 130°) gave/

gave the following results:

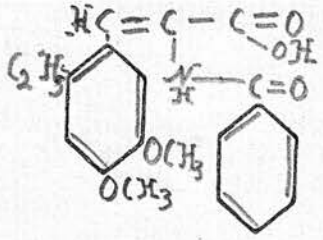
0.1115 gms. of lactone gave 0.0599 gms. of H_2O and 0.290 gms. of CO_2.

Corresponding to 6.01% of H and 71.0% of C.

Calculated for $C_{20}H_{19}O_4N$ 5.7% H and 71.2% C.

The yield is 40.5 gms. of lactone corresponding to 60%.

3.4.dimethoxy-6.ethyl-1.ethyl-1.benzal-hippuric acid



was obtained in heating a small quantity of the lactone in 1% potassium hydroxide solution for 1 hours. The lactone goes into solution, which becomes almost colourless. On acidification white crystals are formed. Melting point 212° C.

3.4.dimethoxy-6.ethyl-1.phenyl-pyruvic acid.

$C_6H_2(OCH_3)_2.C_2H_5.CH_2.CO.COOH$.

20 gms. of the lactone are boiled in a solution of 30 gms. potassium hydroxide in 100 c.c. of water under a reflux. An air current is passed over the boiling liquid and the ammonia evolved neutralised by normal hydrochloric acid, the indicator acting as a control. 53 c.c. of acid were neutralised after 3 hours, equivalent to 94% of the ammonia present. The solution was acidified with sulphur dioxide and cooled/

cooled. The benzoic acid formed could be filtered off. The ketoacid remained in solution, forming a complex salt with the potassium bisulphite. After filtering, the solution was acidified with hydrochloric acid and heated under reduced pressure so as to remove the sulphur dioxide. A crystalline precipitate was formed, recrystallisable out of hot glacial acetic acid and out of alcohol. The precipitate, which was first partly strongly coloured crystallised out in prisms, which were only slightly yellow coloured and melted at 181° C. The yield was 10 gms. = 71%.

3.4.dimethoxy-6.ethyl-1.phenyl-acetic acid.

$C_6H_2(OCH_3)_2.C_2H_5CH_2COOH$.

10 gms. of the keto acid were dissolved in a large excess of dilute sodium hydroxide, and whilst cooling in ice 37 c.c. of a 3% solution of hydrogen peroxide were added, and the solution left in the ice-chest overnight. After neutralisation with sulphur dioxide (to keep unchanged keto acid in solution) the phenyl-acetic acid derivative separated as a slightly brownish coloured oil, which solidified after a day, forming bundles of small prisms. The acid was extracted with ether from the aqueous solution, dried, and the ether ~~dried and~~ evaporated. The acid crystallised in slightly pink coloured bundles of needles/

needles, melting at 67°C. Yield: 7 gms. = 78%. The equivalent of the acid was measured by dissolving it in N/10 sodium hydroxide and titrating back the excess of alkali used with sulphuric acid of known strength. Indicator - phenolphthalein.

0.078 gms. of acid corresponded to 21.6 c.c. of 0.0163 N H_2SO_4 showing an equivalent weight of 222.5.

Equivalent weight calculated for $C_{12}H_{16}O_4$ = 224.

The different reactions described were repeated so as to prepare a larger amount of dimethoxy-ethyl-phenylacetic acid for the further reactions and for the analysis of the substances.

Preparation of 6-nitro-methyl-vanillin.

Methyl vanillin has been prepared and described before in the synthesis of acetoveratrone.

6.nitro-3.4.dimethoxy-benzaldehyde.

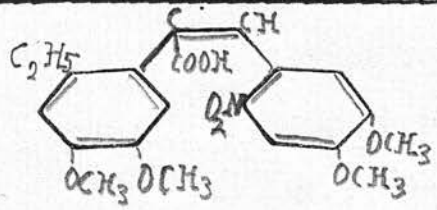
$C_6H_2(OCH_3)_2.NO_2CHO$. (Pschorr)[30]

32 gms. of finely powdered methyl vanillin were slowly added to double the weight of concentrated nitric acid, which was stirred and cooled by ice. The aldehyde dissolved slowly in the nitric acid, forming a dark red, thick liquid. On addition of ice, the nitro-aldehyde separated as light yellow voluminous substance, which was separated from the acid/

acid by filtering through a Buchner funnel. The aqueous solution contained some unchanged aldehyde crystallising out after longer standing, whilst the precipitate after several recrystallisations from hot alcohol formed yellow crystals of which the melting point was 133° C.

Synthesis of the Phenanthrene Derivative.
(Mayer and Balle[31] : Pschorr[32]).

α-(3.4.dimethoxy-6.ethyl-1.phenyl-)β(3.4.dimethoxy-6.nitro-1.phenyl) acrylic acid.



To form the potassium salt of the dimethoxy-ethyl-phenylacetic acid, which was needed in completely dry form for the synthesis, potassium hydroxide in methyl alcohol was added to the alcoholic solution of this acid until the solution was neutral to litmus. The alcohol was then evaporated on the water-bath, and afterwards the salt dried in the vacuum at 120-130° C. for 3 hours. To the potassium salt, which was prepared in a small round bottom flask in this way out of 5 gms. of the acid, 10 gms. of nitro-methyl-vanillin, 8 c.c. of acetic anhydride and 0.2 gms. of anhydrous zinc chloride were added. The flask was fitted with a long tube as air condenser and dry nitrogen gas was very slowly passed over the reaction mixture to prevent oxidation. The flask was heated for 20 hours on an oil-bath to 120° C.

The condensation was then stopped and 20 c.c. of water were added and the solution was heated for an hour on the water-bath. It was then made alkaline/

alkaline with ammonia, and after cooling was filtered. A brown tar remained which was again extracted several times with ammonia. For removal of impurities the ammonia solution was heated to boiling temperature with a small quantity of animal charcoal and filtered after cooling.

The dark yellow coloured solution was now acidified with dilute sulphuric acid. A voluminous yellow precipitate was formed which was filtered, dried, and weighed. The ~~crude~~ yield of the crude acid was 5 gms. = 52%.

The acid was recrystallised from hot dilute methyl alcohol. Yellow crystals were formed which sintered at 203° C. and melted at 208° C.

Equivalent weight.

The acid, which was dried at 110° C. was dissolved in N/70 sodium hydroxide and retitrated by 0.0163 sulphuric acid. The indicator was phenylphthalein. The yellow coloured solution rendered the determination of the neutral point difficult.

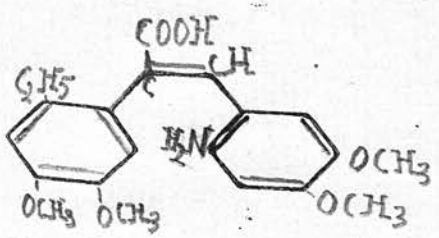
0.0376 gms. nitro acid is equivalent to 8.43 c.c. of 0.0163 N. H_2SO_4

This corresponds to an equivalent of 418.3.

Calculated for $C_{21}H_{22}O_8N$ = 416.2.

Reduction/

Reduction to the amino acid.



2.08 gms. of nitro acid ($\frac{1}{200}$ mol) were dissolved in 20 c.c. of dilute ammonia and heated on the water-bath to 80° C. Then the solution was slowly added to a reduction mixture, heated to the same temperature, which was prepared out of 9.2 gms. ferrous sulphate ($\frac{6}{200}$ mol + 10%) in a little water to which 8 c.c. of 25% ammonia were added. The mixture was shaken and then left standing for two hours on the water-bath, the black iron oxide settling down slowly. The solution was separated from the iron oxide by filtration. It was a dark brown solution, out of which, on addition of dilute acetic acid, a strongly yellow precipitate separated, which was soluble in strong acid and alkali.

The precipitate, which without recrystallisation, after washing and drying, melted at 192°C., gave with sodium nitrite a diazo-compound, forming with β-naphthol in alkaline solution a coloration of deep red.

Formation of the phenanthrene ring.

0.93 gms. ($\frac{1}{400}$ mol) of the amino acid were dissolved in water with the calculated quantity of sodium carbonate. 2½ c.c. of a normal sodium nitrite solution were added and this solution was dropped/

dropped very slowly into 9 c.c. of a well cooled and stirred solution of 5% N. sulphuric acid. This solution of the diazonium salt is filtered and heated for about two hours on the water-bath, until the coupling reaction with alkaline β-naphthol (intense red coloration) was no longer positive. The solution was made slightly alkaline with sodium carbonate and filtered. On acidification with hydrochloric acid a reddish brown acid precipitated. It was filtered and attempts were made to recrystallise it which were unsuccessful. Yield (crude) 0.5 gms.

In another experiment with a small quantity the amino- acid was dissolved in about normal alcoholic hydrochloric acid and diazotised with amyl nitrite. The alcoholic solution was then poured into 60 times its volume of water and copper powder (which had been first washed with ether) was added to catalyse the reduction (as indicated by Pschorr). After standing overnight the solution which no longer gave a colour reaction with alkaline β-naphthol was made alkaline and filtered. To remove amyl alcohol the alkaline solution was extracted with ether. Afterwards the acid was extracted with ether, after adding dilute hydrochloric acid to the solution. The residue from the ether solution which was very small could not be recrystallised.

Removal/

Removal of carbon dioxide.

200 mgms. of the acid were heated in the vacuum in a very small distilling flask. At the bath temperature of 230-250° C. a distillate of oily drops was formed (9 mm. pressure). The distillate was dissolved in ether, extracted with sodium dioxide and the ether evaporated. The residue crystallised out of hot methyl alcohol, forming light brown plates melting at 106° C. A mixed melting point with the ethyl tetramethoxy-phenanthrene, prepared by decomposition of laurotetanine, of which the melting point is 120° C., was 112°.

The product, of which about 30-50 mgms. were present, was distilled in the vacuum, when it distilled at a bath temperature of 230-240° C. The distillate was again recrystallised out of methyl alcohol, in which it showed the same slight solubility as the ethyl and vinyl compound, decomposed from laurotetanine. The crystals, which now were completely colourless melted at 118° C. but the mixed melting point was at 106° C.

The quantity of the substance after recrystallisation did not allow an analysis to be made and was just sufficient to repeat twice the melting points.

The decision as to the identity or diversity of the synthetic product and the product prepared by decomposition can only be given after having prepared the synthetic ethyl tetramethoxy-phenanthrene and/

and the phenanthrene carboxylic acid in a rather larger quantity by repeating the synthesis described. To prove the closing of the phenanthrene ring, possibly the oxidation with nitric acid yielding benzene-tetracarboxylic acid (Warnat [33]) would be useful.

Hofmann Decomposition of N-methyl-laurotetanine-ethyl-ether.

The object of this decomposition is to obtain ethyl-ethoxy-trimethoxy-phenanthrene in which the position of the ethoxy group could be settled by synthesis for the purpose of determining the position of the phenol group in the alkaloid.

The decomposition was done with a quantity of alkaloid which was only obtained and extracted towards the end of these investigations.

Laurotetanine-ethyl-ether.

1.95 gms. ($\frac{1}{200}$ mol) of laurotetanine were dissolved in absolute alcohol and the calculated quantity of sodium (0.115 gms) was added. After all the sodium was dissolved, 1.01gms. of ethyl toluene sulphonate which had previously been distilled in the vacuum were brought into the flask and the alcoholic solution was left for 4 hours under a reflux water-bath. After that time crystals of sodium toluene sulphonate separated. The solution was left standing overnight. Then the alcoholic solution was filtered, leaving the pure crystals of the sodium salt behind. The alcohol was evaporated, the alkaloid dissolved in hydrochloric acid and made alkaline with sodium hydroxide. The ethylated base could thus be extracted with ether, whilst a very

small/

small amount of unchanged phenolic base remained in aqueous solution out of which it was precipitated by ammonium chloride. The ether extract of the laurotetanine ethyl ether was dried and concentrated. The base formed a yellow mass, solidifying from yellow oily consistence without crystallising. It could not be crystallised. Yield: 1.3 gms.

A small amount of the ethyl-laurotetanine was dissolved in acetic acid and by addition of potassium iodide transformed into the iodide of the base, which could be crystallised out of hot water. It forms bundles of almost colourless prisms melting at 198-200° C.

Laurotetanine-ethyl-ether-methiodide.

1 gm. of laurotetanine-ethyl-etherwas heated in a sealed tube with excess of methyl iodide on the water-bath for three hours. It was afterwards treated with water, in which the product was insoluble and extracted from acid solution with chloroform. The dark brown chloroform residue, after washing with ether (as in the case of the glaucine derivative) crystallised in colourless crystals out of acetone. The methiodide, which is insoluble in water, melted at 223-226° C. Yield: 0.6 gms.

Laurotetanine-ethyl-ether-methine-methiodide.

0.5 gms. of the ethyl-ether-methiodide were decomposed by alcoholic potassium hydroxide. The decomposed/

decomposed base crystallised at once after neutralisation in water with acid, forming an insoluble methine-iodide. Without isolating it, the methine was extracted after making alkaline with ammonia. Methyl iodide was added at once to the dried ether extract and a completely white precipitate of laurotetanine-ethyl-ether-methine-methiodide crystallised out. It melted at 275° C. Yield: 0.37 gms.

Vinyl-trimethoxy-ethoxy-phenanthrene.

The methine methiodide decomposed, heated with alcoholic potassium hydroxide, giving off trimethylamine, which was neutralised by hydrochloric acid. After neutralisation and addition of water, insoluble plates of the vinyl compound could be filtered off, which melted at 139° C. after recrystallisation from hot methyl alcohol. The yield of 0.19 gms. corresponds to 79%. The compound decolorised permanganate solution.

Ethyl-trimethoxy-ethoxy-phenanthrene.

The vinyl compound was dissolved in glacial acetic acid and reduced with hydrogen in presence of palladium as catalist. After the reduction, water was added to the solution, precipitating the ethyl compound and the palladium, which was in suspension. It was filtered. The precipitate was extracted with hot methyl alcohol, in which appeared after filtering

and/

and cooling colourless crystalline plates.

Nitro-ethyl vanillin.

6.nitro-ethyl-vanillin was prepared with the purpose of synthesising one of the two alternatives for the ethyl-trimethoxy-ethoxy-phenanthrene.

Ethyl-vanillin was obtained in a yield of 80% by adding slowly to an alcoholic solution of vanillin and an excess of ethyl iodide, the corresponding quantity + 10% of a concentrated potassium hydroxide solution, and heating for 3 hours on the water-bath. The solution separated after addition of water into two layers. The ethyl ether was extracted with ether and purified by distillation in the vacuum in an Anschutz flask. The pure ethyl vanillin melted at 64° C.

6.nitro-ethyl-vanillin was prepared similarly to the methyl compound (Pschorr (34)). One part of powdered ethyl vanillin was added to a solution consisting of one part of fuming nitric acid and one part of commercial concentrated nitric acid, whilst the solution was strongly cooled and stirred. Towards the end of the reaction, the solution, which was dark red, solidified at once. Water was then added in excess, to prevent the nitric acid reacting further

and/

and the yellow precipitate was filtered. It was recrystallised out of alcohol and purified by vacuum distillation, distilling at a bath temperature of 200-210° C. The strongly yellow crystals melt at 159-160° C.

Combustion. For purification the nitro-ethyl-vanillin was sublimed in the vacuum at a temperature of 130-140° C. A silver spiral was used for the reduction of the nitrous vapours during the combustion.

0.0986 gms. of nitro-ethyl-vanillin yielded 0.1929 gms. of CO_2 and 0.042 gms. of H_2O

Corresponding to	53.35% C. -	4.77% H.
Calculated for $C_{10}H_{11}O_5N$	53.33% C. -	4.80% H.

The phenylhydrazone of 6.nitro-ethyl-vanillin prepared by heating the aldehyde with phenyl-hydrazine in glacial acetic acid, crystallises in intensely red crystals. Recrystallised out of alcohol, they melt at 202° C.

Condensation of Nitro-ethyl-vanillin with potassium dimethoxy-ethyl-phenylacetate.

This condensation was carried out as indicated for methyl vanillin.

7 gms. of acid, neutralised and dried in alcoholic solution, were heated with the double amount of nitro-ethyl-vanillin in acetic anhydride with/

with an addition of 0.1 gms. of dry zinc chloride for 15 hours. After hydrolysis of the acetic anhydride and neutralisation with ammonia, a large quantity of yellow crystals remained undissolved. They melted at 159° C. and were identified as unchanged nitro-ethyl-vanillin.

A small quantity of an acid, melting at 196° C. could be isolated. The experiment was repeated with 5 gms. of acid and 10 gms. of aldehyde, when the solution was heated for about 10 hours to 125° C. and then for a short time to about 140-150° C. After purification a yellow acid separated, which was recrystallised. The melting point was 196° C.

The equivalent was determined by dissolving it in N/70 alkali and backtitrating of the unused base.

The equivalent which was about 380 did not correspond with the theoretical weight of 430. Its identity has to be established before further steps towards the synthesis of the ethyl-trimethoxy-phenanthrene can be undertaken.

I wish to express my thanks to Professor Barger for the personal interest he took in my work, where his advice and criticisms were of great value.

R Silberschmidt

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